The disclosure has been amended to correct the informalities cited by the Examiner in page 2 of Paper No. 10 and to obviate the Examiner's objection to the disclosure. Withdrawal of the objection is requested. No new matter has been added.

The applicants note that the specification refers to the trade mark FACS STAR PLUS at page 13. It is capitalized and accompanied by generic terminology (i.e., "flow cytometer"), accordingly, no amendment is believed necessary. Should the applicants be incorrect in their review of the specification, the Examiner is respectfully requested to note where other references to trade marks are located, and appropriate revision will be made.

Claims 1-3 stand rejected under 35 U.S.C. § 112, first paragraph. The Examiner asserts that the specification provides no probative evidence to show the utility of the method claimed. Claims 4 and 5 stand rejected under 35 U.S.C. § 101 as the Examiner believes the claims are drawn to an invention of such incredible utility as to create a strong presumption of inoperativeness that can only be overcome by clear objective evidence. The rejection under Section 112 and the rejection under Section 101 are treated together and the applicants urge

the Examiner to reconsider and withdraw the rejections of the claims in view of the following remarks.

In vivo data demonstrating the utility of the claimed methods have not been generated. However, the applicants have used in vitro assays, i.e. determination of HIV-1-induced cell syncytia formation and viral reverse transcriptase production by inoculated cells, to demonstrate operability. These assays utilize living cells and are widely accepted as accurate models that can reproducibly and effectively predict for example, infectivity and pathogenicity of HIV-1 *in vivo*.

Further, the following evidence is available showing that anti-CD44 antibodies, soluble CD44, or other gene products of CD44 are useful in preventing or treating HIV-1 infection in humans:

a. Recombinant soluble CD44 can prevent HIV-1(BaL) infection of human monocytes and tissue macrophages *in vitro*.

b. Transfection of cells of the CD4 positive/CD44 negative T cell line Jurkat with different isoforms of CD44 causes expression of the expected membrane CD44 protein isoforms. Moreover, the transfected cells have dramatically modified susceptibility to infection with HIV-1. Those cells transfected with and expressing CD44H are essentially not infectable with HIV-1 (despite still expressing CD4), and those transfected with and expressing CD44E have an approximate 9 fold enhancement of infectability with HIV-1. The non-transfected Jurkat cells and those transfected

> with CD44H and CD44E have comparable abilities to bind HIV-1 gp120, despite the widely different susceptibilities to infection. Cells transfected with a truncated form of CD44H (lacking the cytoplasmic domain of the molecule) do not differ from non-transformed Jurkat cells in their susceptibility to HIV-1 infection. This suggests that the cytoplasmic domain is critical in determining the biology.

Thus, *in toto*, these results indicate that anti-CD44 antibodies, soluble CD44, or hyaluronate are useful in preventing or treating HIV-1 infection in humans. Furthermore, CD44H (either soluble molecule, or that expressed endogenously in cells) is predicted to prevent or treat HIV-1 infection.

Should the Examiner find that this data would be more convincing if submitted in the form of a Rule 132 Declaration, she is requested to so indicate and one will be provided.

For the Examiner's convenience and information a copy of an abstract detailing these data is included.

In view of the above, the rejection of claims 1-3 under Section 112 and the rejection of claims 4 and 5 under Section 101 should be withdrawn.

Claims 1-3 stand rejected under 35 U.S.C. § 103 over Haynes in view of St. John. The Examiner asserts that it would have been prima facie obvious at the time the present invention was made to combine the teachings of Haynes on the role of the

CD44 adhesion molecule with the teachings of St. John on the polypeptides and other epitopes useful in therapeutic compositions of the leucocyte adhesion molecule, "with the expectation of a method of suppressing T cell activation in an animal, inhibiting CD44 monocyte-mediated IL-1 release and treating inflammation with the further expectation that the method would be effective in reducing inflammation, inhibiting IL-1 release and suppressing T cell activation in an animal." Reconsideration is requested in view of the following.

The Examiner's rejection of the claims as obvious is wholly inconsistent with her rejection of the claims as nonenabled and as lacking utility. Further, the Examiner's rationale for combining the references is at odds with her statements with respect to the prior rejections. Accordingly, it is submitted that the rejection is clearly in error and should be withdrawn.

Claims 1-3 stand provisionally rejected under 35 U.S.C. § 101 as allegedly claiming the same invention as that of claims 1-3 of application Serial No. 07/669,730. Claims 1-3 also stand provisionally rejected under 35 U.S.C. § 102(e) over copending application Serial No. 07/669,730. Abandonment of application Serial No. 07/669,730 renders these rejections moot. The

Examiner's attention is, however, directed to pending Application No. 07/973,339.

In view of the above, the instant application is submitted to be in condition for allowance and an early Notice is respectfully requested.

Respectfully submitted,

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DIFFERENTIAL MODULATION OF HIV-1 INFECTION OF A T CELL LINE BY EXPRESSION OF TRANSFECTED CD44E AND CD44H ISOFORMS. ED Rivadeneira,* H-X Liao,* DL Sauls,* BF Haynes, and JB Weinberg. VA and Duke University Medical Centers, Durham, NC.

HIV-1 infection of susceptible cells is largely dependent on binding of viral gp120 to cellular CD4. In earlier work, however, we noted that antibodies against the transmembrane protein CD44 inhibited infection of mononuclear phagocytes. Different isoforms of CD44 appear to be important in hyaluronate binding, in leukocyte homing, in establishing tumor cell metastases, and in modulation of lymphocyte and monocyte function. The purpose of this study was to determine the effects of transfection of the CD4 positive-CD44 negative Jurkat T cell line with cDNA for CD44E or CD44H, two different isoforms of CD44. Cells transfected with CD44E displayed high levels of cell surface CD44E with less surface CD4 than Jurkat-parent cells, and grew to similar densities. Although the Jurkat-parent cells and Jurkat-CD44E transfectants could not be infected by the monocytotropic virus strain HIV-1$_{BaL}$, both cell lines were successfully infected by the lymphocytotropic virus strain HIV-1$_{IIIB}$. Jurkat-CD44E cells were more susceptible to infection with HIV-1$_{IIIB}$, as compared to the Jurkat-parent cells. They had earlier syncytia formation, and had higher levels of viral reverse transcriptase. At 9 days after inoculation, the ability of HIV-1$_{IIIB}$ to infect the Jurkat-CD44E cells was approximately 9 times greater than that for the Jurkat-parent cells as determined by $TCID_{50}$. In contrast to Jurkat-parent and Jurkat-CD44E cells, Jurkat-CD44H cells were much less susceptible to HIV-1 infection displaying no evidence of infection at day 9, despite expressing high levels of CD4. All three cell lines bound gp120 equally well, suggesting that CD44 modulation of HIV-1 infection-expression was independent of gp120-CD4 binding. Expression of different cellular CD44 isoforms appears to be an important determinant of HIV-1 infection and expression *in vitro*.

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